ORIGINAL ARTICLE

Triple Contractile Imaging in the Stress Echo Lab: the Additive Prognostic Value of Pressure–Volume and Preload Recruitable Stroke Work Relationships

Triple imagen contráctil en el laboratorio de ecoestrés: el valor pronóstico adicional de las relaciones presión-volumen y trabajo latido reclutable por precarga

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ABSTRACT

Background: Stress echo positivity based on regional wall motion abnormalities has been declining as new positivity criteria based on left-ventricular contractile reserve (stress/rest ratio of left-ventricular elastance) have been proposed. In addition, the slope of preload-recruitable stroke work, i.e. the slope of the relationship between ventricular stroke work and end-diastolic volume, provides a preload and afterload independent measure.

Objective: The aim of this study was to assess the incremental prognostic value of left-ventricular contractile reserve and of the slope of preload-recruitable stroke work.

Methods: A total of 692 patients (62±12 years) with negative stress echo (exercise n=130; dipyridamole n=438; dobutamine n =124) and no dilation (n=470) or idiopathic dilated cardiomyopathy (n=222) were selected from the Stress echo multicenter study CNR data bank. All underwent triple imaging to assess: 1- wall motion abnormality 2- left-ventricular contractile reserve and 3- the slope of preload-recruitable stroke work.

Results: By selection, all patients had negative stress echo by wall motion abnormality criterion. The overall positivity rate was 49 % for contractile reserve, 36 % for the slope of preload-recruitable stroke work (positivity criteria ≤ 64 erg×cm−3×103), 19% for both criteria positivity and 33 % for both criteria negativity. In the 692 patients with median follow-up of 20 months, there were 132 events. Event rate was lowest in patients with double negativity, and highest in those with double positivity (X2 = 51, p<0.001).

Conclusions: The stress echo positivity rate and prognostic yield are sharply increased if the stress contractile reserve and the resting slope of preload-recruitable stroke work are added to conventional regional wall motion abnormalities.

Keywords: Stress echocardiography - Triple imaging - Contractility - Preload - Starling.

RESUMEN

Introducción: La positividad del ecoestrés a través de alteraciones de la motilidad parietal ha ido cediendo terreno frente a nuevas propuestas basadas en la reserva contráctil del ventrículo izquierdo (índice stress/reposo de la elastancia ventricular izquierda). Por otra parte, la pendiente del trabajo latido reclutable por precarga, es decir, la pendiente de la relación trabajo latido y volumen de fin de diástole proporciona una medida independiente de la precarga y la poscarga.

Objetivo: El propósito de este estudio fue evaluar el valor pronóstico adicional de la reserva contráctil ventricular izquierda y la pendiente del trabajo latido reclutable por precarga.

Métodos: Se seleccionaron 692 pacientes de la base de datos del estudio multicéntrico de ecoestrés del Consejo Nacional de Investigaciones (Consiglio Nazionale delle Ricerche, CNR), con edad media de 62 ± 12 años, ecoestrés negativo (ejercicio = 130; dipiridamol = 438; dobutamina n = 124) y sin dilatación (n = 470) o miocardiopatía idiopática dilatada (n = 22). Todos los pacientes fueron sometidos a triple imagen: 1) evaluación de alteraciones de la motilidad parietal; 2) evaluación de la reserva contráctil ventricular izquierda; y 3) evaluación de la pendiente del trabajo latido reclutable por precarga.

Resultados: De acuerdo a la norma de selección, todos los pacientes tuvieron un estudio de ecoestrés negativo según el criterio de motilidad parietal alterada; la tasa de positividad global fue de 49% para la reserva contráctil, 36% para la pendiente del trabajo latido reclutable por precarga (criterio de positividad ≤ 64 erg × cm−3 × 103), 19% para ambos criterios de positividad y 33% para ambos criterios de negatividad. En los 692 pacientes con una mediana de seguimiento de 20 meses, hubo 132 eventos. La tasa de eventos fue menor en pacientes con doble negatividad y mayor en aquellos con doble positividad (X2=51, p<0,001).

Conclusiones: La tasa de positividad del ecoestrés y el rendimiento pronóstico aumentan marcadamente si la reserva contráctil con estrés y la pendiente del trabajo latido reclutable por precarga se suman a las alteraciones de motilidad parietal regional convencionales.

Palabras clave: Estrés, ecocardiografía - Triple imagen - Contractilidad - Precarga - Starling

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Abbreviations

EDV	End-diastolic volume	**RWMA**	Regional wall motion abnormalities
ESPVR	End-systolic pressure–volume relationship	**SBMw**	Single-beat slope of preload-recruitable stroke work
LVCR	Left ventricular contractile reserve	**SE**	Stress echocardiography
PRSW	Preload-recruitable stroke work	**WMSI**	Wall motion score index

INTRODUCTION

Starting in 2003 we introduced the end-systolic pressure–volume relationship (ESPVR) in the stress echo (SE) lab by using the ESPVR at increasing heart rates (1). The ESPVR is easily obtained during routine stress echocardiography and has been established as an afterload independent index of left ventricular contractility (2). As most indexes of contractility the ESPVR is preload dependent (3). Recently, a new candidate index was proposed, with appealingly strong theoretical and experimental basis and potentially amenable to noninvasive assessment in the echo lab, both at rest and during stress (4, 5): the preload-recruitable stroke work (PRSW) relationship, which is defined as the relationship between ventricular stroke work and end-diastolic volume (EDV) (6). It can often be derived from the same set data used for determining the ESPVR and provides an even less load-dependent measure of left ventricular contractility. An accurate assessment of the intrinsic ventricular contractile state that is independent of preload and afterload deepens and broadens the understanding of the pathophysiology of cardiovascular diseases and thereby helps enable effective diagnoses and treatment (5). Unlike the ESPVR, the PRSW relationship is difficult to directly link with arterial loads in the pressure-volume plane, but due to its strong linearity over a wide range of physiological loads and independence of chamber size, (7) it compensates for potential limitations of the ESPVR. The aim of this study was to estimate the ESPVR and PRSW relationship from a single control beat under various haemodynamic conditions in humans undergoing stress echo (SE) with negative stress echocardiography, and to evaluate their clinical applicability and prognostic impact in a clinically realistic environment and in patients in whom we need most the information on global left ventricular contractility, i.e. those with absence of regional wall motion abnormalities (RWMA) during stress (who may still be at intermediate risk).

METHODS

Patients

From January 2003 to 2013, 1,174 patients underwent stress echocardiography in four quality-controlled stress echo laboratories (Cesena, Bergamo, Mestre and Belgrade). The study protocol was approved by the institutional ethics committee, and before the test, an informed consent was obtained from all patients (or their guardians). Stress echo data were collected and analyzed by stress echocardiography specialists not involved in patient care. Exclusion criteria were congenital or valve heart disease (n=74), unsatisfactory imaging of the left ventricle (LV) at rest or during stress (n=41), wall motion score index (WMSI) >1 at rest (n=199) [but including idiopathic dilated cardiomyopathies (IDCM)], atrial fibrillation (n=18), positive SE (n=118), or no available follow-up data (n=32). Thus, the study population included 692 patients, 431 (62%) men and 261 (38%) women, with mean age of 62±12 years, left ventricular ejection fraction (LVEF) 50±17% (Table 1), negative SE by wall motion criteria and follow-up data. Patients were categorized ex-post as idiopathic dilated cardiomyopathy, n=222; known coronary artery disease (CAD), n=192 or diagnostic tests, n=278. Diagnostic tests were stress tests in patients with low pretest probability of coronary artery disease, ECG abnormalities at rest or exercise electrocardiography, and no left ventricular dilation (Table 1).

Echocardiographic Baseline measurements

The following basic variables were measured from the parasternal long-axis view: left ventricular end-diastolic and end-systolic dimensions (mm), interventricular septal thickness (mm), and left ventricular posterior wall thickness (mm). Left ventricular mass was measured according to the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommendations with the ASE-cube left ventricular mass method (4), and values expressed in g/m2.

Stress echocardiography

Transthoracic stress echocardiography studies were performed with commercially available ultrasound machines (iE 33 and Vivid System 7). All readers had passed upstream preliminary quality control of SE reading. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with semi-supine exercise (n=130), dobutamine (n=124), or high-dose dipyridamole (up to 0.84 mg over 6 min, n=438) (8, 9). Echocardiographic images were semi-quantitatively assessed using a 17-segment, 4-point scale model of the LV. A WMSI was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced wall motion abnormality. By selection, all patients had a negative SE test by wall motion criteria (peak WMSI ≤ rest WMSI) (8, 9).

Volume Analysis and Blood Pressure Analysis

Left ventricular end-diastolic and end-systolic volumes were measured from apical four- and two-chamber views, using the biplane Simpson method (10). Only representative cycles with optimal endocardial visualization were measured and the average of three measurements was taken. The endocardial border was traced, excluding the papillary muscles. The frame captured at the R wave of the ECG was considered to be the end-diastolic frame, and the frame with the smallest left ventricular silhouette the end-systolic frame. The blood pressure recording was made using a sphygmomanometer and the diaphragm of a standard stethoscope. End-systolic pressure was calculated as 0.9 × brachial systolic blood pressure, a noninvasive estimate of end-systolic pres-

Table 1. Clinical and echocardiographic findings of the study population

Clinical findings	
Age (years)	62±12
Male sex	431 (62%)
Diagnostic tests, WMSI at rest = peak = 1±0	278 (40%)
Known coronary artery disease, WMSI at rest = peak = 1±0	192 (28%)
Prior myocardial infarction (STEMI n = 22; NSTEMI n = 20; primary PCI n = 29)	42 (6%)
Prior coronary artery bypass grafting, n = 12	12 (2%)
Elective prior coronary revascularization, PCI n = 64	93 (13%)
Idiopathic dilated cardiomyopathy, resting WMSI = 2.23±0.34; peak WMSI = 1.94±0.47	222 (32%)
Diabetes	84 (12%)
Arterial hypertension	291 (42%)
Left bundle branch block	116 (17%)
Therapy at time of test	
Betablockers	286 (41%)
Calcium antagonists	91 (13%)
Nitrates	60 (9%)
ACEIs or ARBs	309 (45%)
Diuretics	227 (33%)
At least one medication	465 (67%)
Resting and stress echo findings	
Left ventricular mass index (LVMI, g/m2)	120±38
Resting LV ejection fraction (%)	50±17
Peak LV ejection fraction (%)	58±18
Resting wall motion score index (ratio)	1.40±0.61
Peak wall motion score index (ratio)	1.30±0.51
Resting heart rate (beats/min)	72±14
Peak heart rate (beats/min)	104±26
Resting end-systolic pressure (mmHg)	118±20
Peak end-systolic pressure (mmHg)	126±32
Resting LV end-diastolic volume (ml)	118±59
Peak LV end-diastolic volume (ml)	110±54
Resting systolic pressure/end-systolic volume index (mmHg/ml/m2)	5.38±3.55
Peak systolic pressure/end-systolic volume index (mmHg/ml/m2)	8.19±6.69
Left ventricular contractile reserve (LVCR, ratio)	1.54±0.88
Dipyridamole stress, LVCR ≤1.1	206 (47%)
Exercise stress, LVCR ≤2	69 (53%)
Dobutamine stress, LVCR ≤2	66 (53%)
Resting stroke Work (mmHg*ml)	6349±2696
Peak Stroke Work (mmHg*ml)	7349±3168
Single-beat preload recruitable stroke work slope (Mw), i.e. SBMw	
Resting SBMw (erg×cm−3×103)	73±28
Peak SBMw (erg×cm−3×103)	87±37
k (constant)	0.729±0.029

Data presented are mean value±SD or number (%) of patients.
WMSI: Wall motion score index. NSTEMI; Non-ST-segment elevation myocardial infarction. STEMI: ST-segment elevation myocardial infarction. PCI: Percutaneous coronary intervention.
ACEIs: Angiotensin-converting enzyme inhibitors. ARBs: Angiotensin receptor blockers. LV: Left ventricular. LVCR: Left ventricular contractile reserve. SBMw: Single-beat slope of the recruitable stroke work relationship. Erg: unit of work, equal to the work done by a force of one dyne when its point of application moves one centimeter in the direction of the action force. k: Ratio of the epicardial shell volumes corresponding to the volume-axis intercept and baseline left ventricular end-diastolic volume.

sure that accurately predicts pressure-volume loop measurements of end-systolic pressure. (11) The indexes of ventricular elastance were calculated as left ventricular end-systolic elastance (Ees) index (Ees) = end-systolic pressure/end-systolic volume index (1). Stroke work (mL × mmHg) was calculated as stroke volume × end-systolic pressure (2) and stroke volume (mL) as end-diastolic volume - end-systolic volume.

Estimation of left-ventricular contractile reserve

The left-ventricular contractile reserve (LVCR) was assessed with the stress/rest ratio of left ventricular elastance (systolic blood pressure by cuff sphygmomanometer/end-systolic volume from apical 4-and 2-chamber views of 2D echocardiography, using the biplane Simpson rule,).

Estimation of the preload-recruitable stroke work relationship

The preload-recruitable stroke work relationship and its slope (Mw) was estimated by a single-beat technique, as reported by Lee et al. (4, 12) Briefly, "single-beat Mw" (SBMw) was calculated as follows: (stroke work)/[EDV−k × EDV + (1− k) × left ventricular wall (erg × cm−3 × 103). End-diastolic volume was derived from 2D echocardiography using the Simpson method. Left ventricular wall was estimated by the echocardiography-derived left ventricular mass. The k constant was calculated by the previously assessed equation: k = 0.0004 × left ventricular mass + 0.6408. (4, 12) This single-beat technique for the preload-recruitable stroke work relationship and its slope has been reported to be well correlated with that obtained by the invasive catheter method for different left ventricular sizes, mass and presence of RWMA (4). Because left ventricular mass equals left ventricular wall × 1.05 (specific gravity of the heart muscle), the left ventricular wall was estimated from the echocardiography-derived left ventricular mass obtained at rest as previously described. A flat preload-recruitable stroke work relationship slope indicates that increased preload produces relatively little increase in stroke work because of reduced contractility. (4, 5)

Follow-up data

Outcome was determined from patient interviews at the outpatient clinic, hospital chart reviews and telephone interviews with the patient, his/her close relatives or referring physician. Major adverse cardiac events (death, heart failure-related hospitalization, non-fatal myocardial infarction, and coronary revascularization by surgery or percutaneous intervention) were considered clinical events. In order to avoid misclassification of the cause of death, overall mortality was considered. Stress echo results related to regional wall motion abnormalities were available to the referring physician, whereas LVCR and the PRSW relationship slope were not available, as they were still considered to be under investigation.

Statistical Analysis

All the data are given as mean ± standard deviation. Statistical analysis was performed with SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). Differences between groups were compared using Student's t and the chi-square test, as appropriate. The receiver operating characteristic (ROC) curve was used to analyze the sensitivity and specificity of the parameters to detect survival. We selected the cut-off values that maximize sensitivity plus specificity. The area under the curve was used to compare predictive parameters. Event rates were estimated with Kaplan-Meier curves and compared with the log-rank test. Annual event rates were obtained from Kaplan-Meier estimates to take censoring of the data into account. Statistical significance was set at $p < 0.05$.

Ethical considerations

The analysis was carried out following the recommendations of Good Clinical Practice Guidelines and current regulations, and with the approval of the Institutional Review Committee.

RESULTS

Stress echocardiography

No major complications occurred during the test. The 222 IDCM patients had resting wall motion abnormality (WMSI=2.23±0.34 at rest; WMSI=1.94±0.47 at peak stress), of which 152 (68%) exhibited viability response to stress. Regional wall motion abnormalities were, by selection, absent at rest and peak stress in all CAD and diagnostic test patients.

Left ventricular contractile reserve

Previously established positivity criteria of LVCR were stress-specific: ≤1.1 for dipyridamole and ≤2.0 for exercise and dobutamine (9). Left ventricular contractile reserve was abnormal in 101 (36%) diagnostic test patients, in 114 (59%) of CAD patients, and in 126 (57%) of IDCM patients.

Preload-recruitable stroke work relationship and its slope (Mw)

The relationship between EDV and ventricular stroke work is reported in Figure 1 for patients at rest and at peak stress. The resting Mw slope was 85±22 erg × cm−3 × 103 in diagnostic test patients with suspected CAD and normal resting left ventricular function; 86±23 erg × cm−3 × 103 in CAD patients; 47±20 erg × cm−3 × 103 in IDCM patients.

Follow-up events

During a median follow-up of 20 months (1st quartile 8 months, 3rd quartile 40 months), 132 events were registered: 41 deaths (36 cardiac and 5 non-cardiac), 57 heart failure hospitalizations, 12 myocardial infarctions, and 22 revascularizations (3 surgical, 19 angioplasties). There were 100 events in patients with abnormal LVCR and 32 in those with normal LVCR (29% vs. 9%; $p<0.0001$). The event rate was higher in patients with IDCM and with CAD.

Single-beat preload-recruitable stroke work relationship and its slope; outcome prediction and comparisons with LVCR

Receiver-operating-characteristic curves, and the corresponding areas under the curve (Figure 2 and Table 2) show the predictive performance of the PRSW relationship slope (Mw) at rest, with a Mw slope cut-off value of ≤64 erg × cm−3 × 103 for all follow-up events and a cutoff value of ≤44 erg × cm−3 × 103 for death. Resting Mw was abnormal in 47 (17%) of 278 patients with suspected CAD, in 30 (16%) of 192 CAD patients, and in 174 (78%) of 222 IDCM patients.

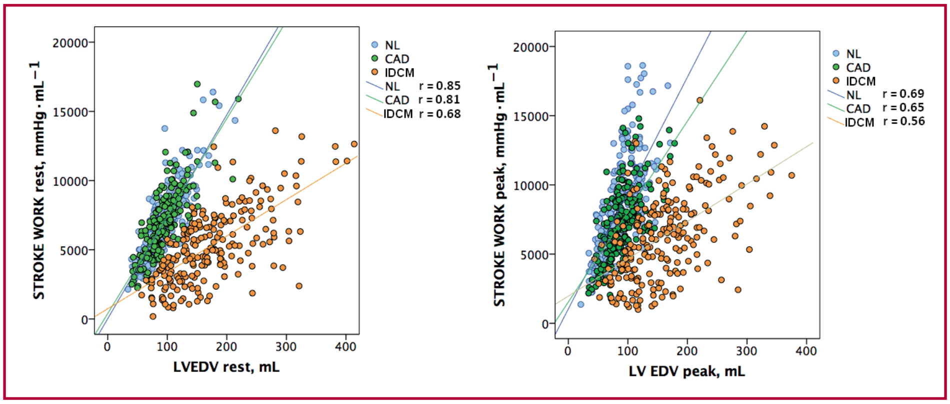


Fig. 1. Linear relationship between left ventricular end-diastolic volume (LVEDV) and stroke work at rest (left) and at peak stress (right). Green and blue circles represent patients with normal left ventricular function and orange symbols patients with left ventricular dilation (IDCM).

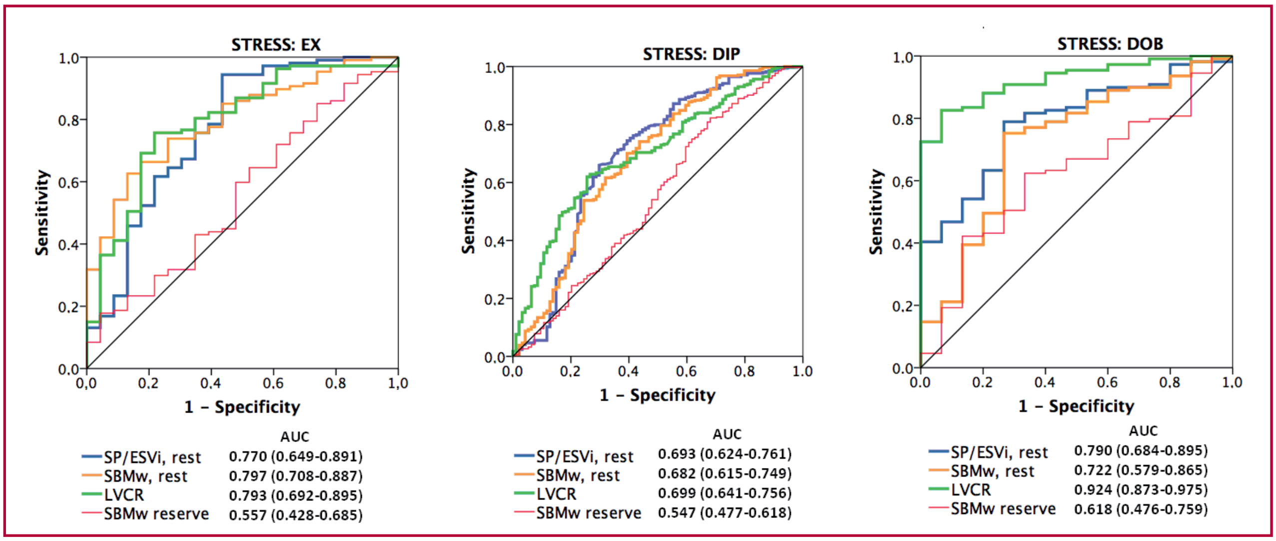


Fig. 2. Receiver operating analysis curves for the best cut-off value of the end-systolic pressure-volume relationship (ESPVR) at rest, of the resting single beat Mw slope (SBMw), of the left ventricular contractile reserve (LVCR) and of the SBMw reserve to predict future events in patients scheduled for exercise (EX), dipyridamole (DIP) and dobutamine (DOB) stress echocardiography. While the LVCR is a better predictor of events vs. baseline ESPVR, the Mw slope reserve (peak/rest ratio) does not increase the predictive power of the Mw slope at rest.

Resting Mw slope was ≤64 erg × cm−3 × 103 in 251 (36%) patients, while LVCR was abnormal in 341 (49%) patients. The two parameters were both abnormal in 131 (19%) patients and normal in 231 (33%) patients. The overall positivity rate was 49 % for LVCR, 36 % for resting Mw, and 19% for any of the 2 criteria combined (with incremental Hazard Ratio of 8.3, 95% CI 4.1-16.7).

Multivariate contractile indicators of major adverse cardiac events

The follow-up event-rate was 43% in patients with both abnormal rest Mw and LVCR, 21% in patients with abnormal LVCR only, 19% in patients with abnormal Mw only, and 4% in patients with both normal Mw and LVCR (Figure 3). When death was considered as clinical end-point, the event rate was 1% in patients with both normal resting Mw slope and LVCR, fivefold higher in patients with abnormal resting Mw or LVCR only, and eighteen-fold higher in patients with both abnormal resting Mw and LVCR (Figure 4). The new indices add significant additional information compared with LVEF at rest and during stress (Figure 5 and Table 3).

DISCUSSION

Both the LVCR and the slope of the PRSW relationship have been used invasively as useful indices of a ventricular contractile property that is relatively insensitive to loading conditions (13). In this study the afterload-independent LVCR, and the preload-independent PRSW relationship and its slope have been estimated non-invasively by the single-beat technique postulated by Lee et al. (4). A flat slope, a low preload-recruitable stroke work relationship, indicates that increased preload produces relatively little increase in stroke work because of reduced contractility (12). The relationship takes both preload and afterload into account and is applicable to a wide variety of cardiac diseases. In the current study, the PRSW relationship and its slope, predicted event-free survival in dilated and non-dilated hearts.

Table 2. Prognostic value of stress-induced variation in left ventricular contractile reserve and Mw reserve in patients with negative stress echocardiography

EXERCISE STRESS ECHO, n = 130	AUC	95% CI	P	Sensitivity	Specificity	Youd Index
Resting SP/ESV index (mmHg/ml/m^2)	0.770	0.649 - 0.891	0.000	94%	57%	1.5
Mw at rest (erg×cm^{-3}×10^3)	0.797	0.708 - 0.887	0.000	63%	87%	1.5
LVCR = Peak SP/ESV index / Resting SP/ESV index (ratio)	0.793	0.692 - 0.895	0.000	76%	78%	1.54
Mw reserve = Peak Mw / Rest Mw (ratio)	0.557	0.428 - 0.685	0.395	-	-	-
DIPYRIDAMOLE STRESS ECHO, n=438	**AUC**	**95% CI**	**P =**	**Sensitivity**	**Specificity**	**Yound Index**
Resting SP/ESV index (mmHg/ml/m^2)	0.693	0.624 - 0.761	0.000	0.66%	0.70%	1.36
Mw at rest (erg×cm^{-3}×10^3)	0.682	0.615 - 0.749	0.000	70%	61%	1.31
LVCR = Peak SP/ESV index / Resting SP/ESV index (ratio)	0.699	0.641 - 0.756	0.000	62%	75%	1.37
Mw reserve = Peak Mw / Rest Mw (ratio)	0.547	0.477- 0.618	0.16	-	-	-
DOBUTAMINE STRESS ECHO, n=124	**AUC**	**95% CI**	**P**	**Sensitivity**	**Specificity**	**Yound Index**
Resting SP/ESV index (mmHg/ml/m^2)	0.790	0.684 - 0.895	0.000	79%	83%	1.52
Mw at rest (erg×cm^{-3}×10^3)	0.722	0.579 - 0.865	0.005	75%	73%	1.49
LVCR = Peak SP/ESV index / Resting SP/ESV index (ratio)	0.924	0.873 - 0.975	0.000	83%	93%	1.76
Mw reserve = Peak Mw / Rest Mw (ratio)	0.618	0.476 - 0.759	0.140	-	-	-

AUC: Area under the ROC curve. SP: Systolic pressure. ESV: End-systolic volume. Mw: Slope of the recruitable stroke work relationship. Erg: Unit of work, equal to the work done by a force of one dyne when its point of application moves one centimeter in the direction of the action force. LVCR: Left ventricular contractile reserve. Youd: Youden.

The anatomic and physiological basis of the k value, and of the preload recruitable stroke work relationship

The underlying rationale for the calculation of the single-beat slope of PRSW is the allometric hypothesis (14). On the basis of the allometry theory, the ratio of the epicardial shell volumes corresponding to the volume-axis intercept and baseline EDV (unstressed volume to stressed volume) was assumed to be a constant k, and this assumption appeared to be valid in the experimental lab in animals and in the clinical setting in humans (4, 5). The individual constant k was estimated by an experimentally and clinically validated equation: k=0.0004 × left ventricular mass + 0.6408 (12). The relative consistency of k values across species and various diseased hearts in humans implies that k values reflect not only anatomic similarity (allometric hypothesis) but also physiological similarity for some fundamental processes of cardiac muscle contraction. The ratio of the cardiac myocyte sarcomere length at zero stroke work (unstressed) to that at end diastole during baseline conditions (stressed) may be one of the major determinants for the individual k value. Prior studies have revealed that at diastole, the cardiac sarcomere length is 2.2 μm during maximally stressed conditions for canines or humans (15). At unstressed conditions, the sarcomere length may vary narrowly from 1.85 to 2.0 μm, due to the restriction from passive force and the restoring force development by titin (16). Therefore, the length ratio of the normal functioning sarcomere at unstressed and stressed conditions is relatively constant, which contributes to the preservation of k values.

Noninvasive applications of the single beat preload-recruitable stroke work relationships technique

The single-beat technique is the foundation for the potential wide application of the PRSW relationships in clinical practice. The calculation of the PRSW relationship requires measurements of baseline stroke

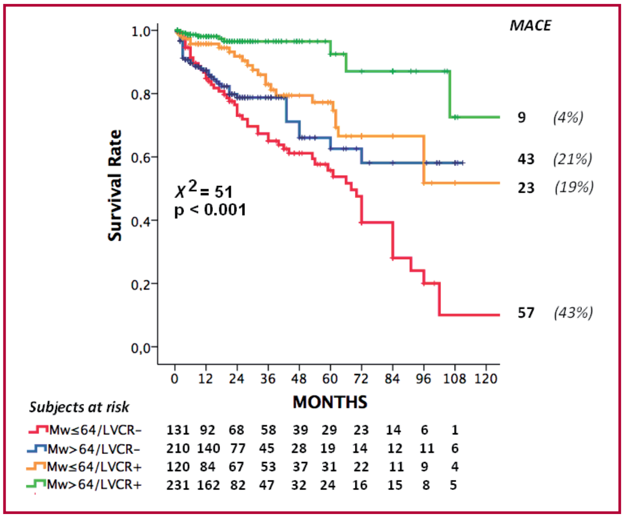


Fig. 3. Kaplan-Meier event-free survival curves in patients with negative stress echo stratified according to Mw > or ≤ 64 erg×cm-3×103, and normal or abnormal left ventricular contractile reserve (LVCR). The prognosis is excellent in double negative, worse in double positive, and intermediate in single positive patients.

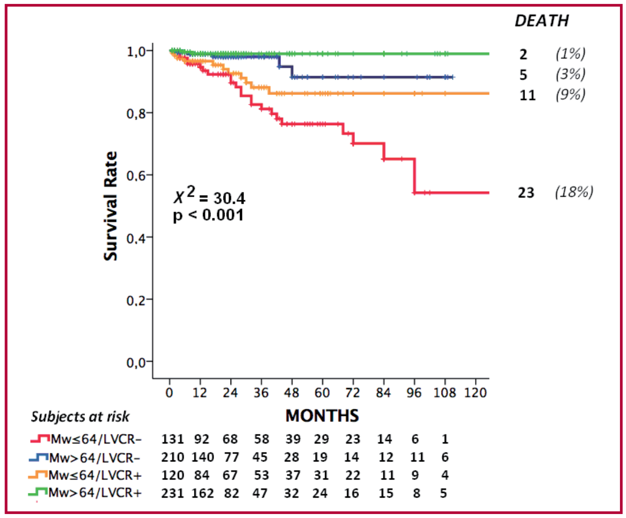
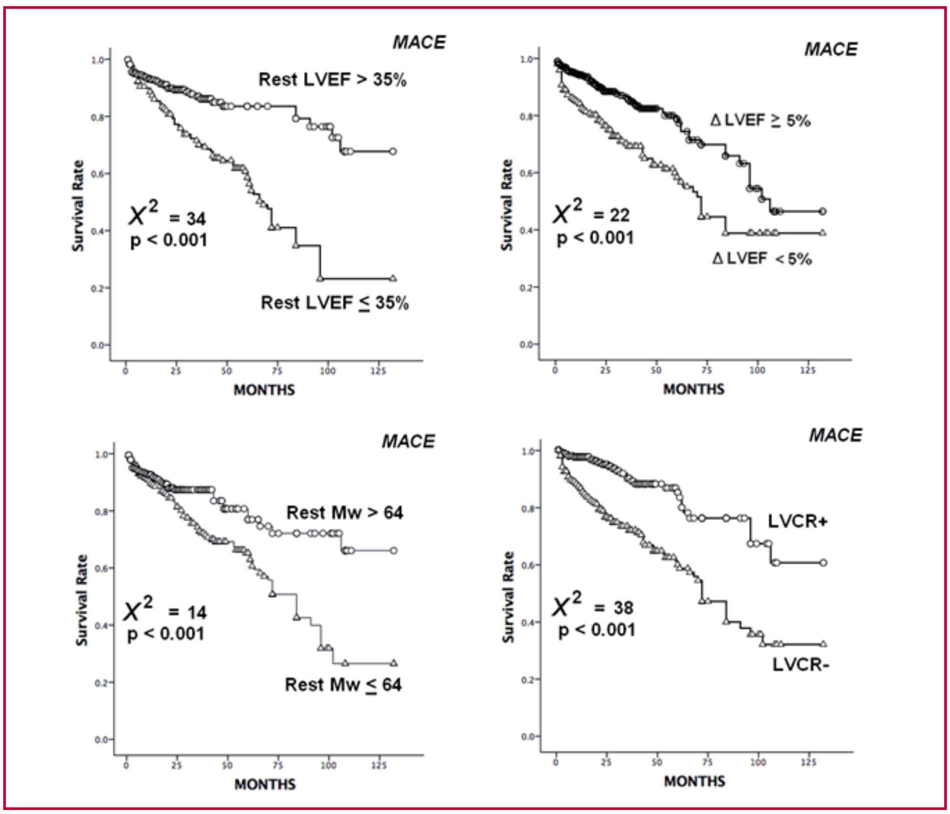


Fig. 4. Kaplan-Meier survival curves in patients with negative stress echo stratified according to Mw > or ≤ 64 erg×cm-3×103 and normal or abnormal left ventricular contractile reserve (LVCR). The prognosis is excellent in double negative, worse in double positive patients.

Fig. 5. Standard vs. new prognostic predictors. Kaplan-Meier survival curves (considering combined death or heart failure hospitalization as endpoint) in medically treated patients. Left upper panel: stratified curve according to the presence of resting left ventricular ejection fraction (LVEF) > 35% as cut-off value. Right upper panel: stratified curve according to stress ΔLVEF ≥ 5% vs. rest as cut-off value. Left lower panel: stratified curve according to resting Mw > or ≤ 64 erg×cm-3×103. Right lower panel: stratified curve according to and normal (+) or abnormal (-) left ventricular contractile reserve (LVCR). MACE: Major adverse cardiovascular events.



work, baseline EDV, and left ventricular mass, all of which can be derived from noninvasive echocardiography and brachial blood pressure measurements. In previous studies, noninvasively derived SBMw was significantly related to invasively derived SBMw using either a constant k (0.72) or an estimated individual k (4, 5).

Associated single-beat techniques for assessment of left ventricular contractility

Because Mw and LVCR describe left ventricular performance in different perspectives, the availability of both techniques should provide a more comprehensive evaluation of left ventricular performance (4, 6, 17, 18). In this study, while the LVCR offers incremen-

Table 3. Univariate and multivariate prognostic predictors (all patients)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.009 (0.992-1.027)	0.297		
Gender (male)	0.870 (0.565-1.339)	0.527		
LVEF at rest (%)	0.960 (0.929-0.992)	0.016	0.964 (0.942-0.987)	0.002
Resting – peak LVEF changes (Δ 5%)	0.944 (0.623-1.431)	0.786		
SP/ESV index at rest (mmHg/ml/m^2)	1.027 (0.903-1.168)	0.686		
LVMI (gr/m^2)	1.005 (1.000-1.011)	0.061	1.006 (1.001-1.011)	0.027
Rest SBMw (erg cm^{-3}x10^3)	1.014 (0.999-1.029)	0.067	1.013 (1.000-1.027	0.051
peak SBMw (erg cm^{-3}x10^3)	0.991 (0.980-1.001)	0.084	0.992 (0.982-1.002)	0.099
LVCR >1.1 DIP; > 2 EX, DOB	0.450 (0.291-0.698)	0.000	0.445 (0.293-0.677)	<0.001

HR: Hazard ratio. LVEF: Left ventricular ejection fraction. SP: Systolic pressure. ESV: End-systolic volume. LVMI: Left ventricular mass index. SBMw: Single-beat slope of the recruitable stroke work relationship. Erg: Unit of work, equal to the work done by a force of one dyne when its point of application moves one centimeter in the direction of the action force. LVCR: Left ventricular contractile reserve. DIP: Dipyridamole. EX: Exercise. DOB: Dobutamine.

tal diagnostic and prognostic information at peak stress echo vs. baseline, the PRSW relationship did not greatly change with exercise or pharmacological stress. The Mw slope reserve (peak/rest ratio) does not increase the predictive power of the resting Mw slope (Fig. 2 and Table 2). Because of the different hemodynamic characteristics, it would be ideal to have both LVCR and the PRSW relationship at rest to enhance clinical interpretation, and both parameters can be obtained during the same echocardiographic examination (19, 20). Global contractility assessment beyond LVEF through LVCR during stress, and new indices such as the slope of PRSW at rest may be clinically useful for identifying patients with suboptimal prognosis in spite of negative stress echo by wall motion criteria, in both very early and very advanced stages of disease. In fact, initial cardiomyopathy (due to diabetes or hypertension or cardiotoxic chemotherapy in oncology patients) can be associated with normal resting and stress regional left ventricular function, yet with an abnormal contractile reserve during stress (21). At the opposite end of the disease spectrum, patients with severe resting left ventricular dysfunction and no change in segmental wall motion score (fixed response at viability testing) can still have a contractile reserve mirrored by the increase in ΔESPVR during stress. If stress is not applied and/or not feasible, the slope of PRWS at rest is more sensitive than LVEF in detecting subtle, yet prognostically significant, alterations in left ventricular function.

Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work

The major advantage of the PRSW relationship vs. the stroke work - end-diastolic pressure relationship is the linearity of the former relationship vs. the curvilinearity of the latter. The Frank-Starling relationship generally has been examined with filling pressure as an index of preload, resulting in a curvilinear function that reaches a plateau at higher filling pressures and is difficult to quantify (6). Given these difficulties, Sarnoff speculated that "a plot of work against volume (or fiber length) would be closer to a straight line." The linearity of the PRSW curve observed in recent studies (4, 5, 12) confirms the speculations of Starling and Sarnoff (19, 20) and indicates that the curvilinear relationship between stroke work and filling pressure results from the exponential nature of the diastolic pressure-volume-relationship. When preload is indexed by EDV rather than pressure, the relationship between stroke work and preload is linear (5, 20). The PRSW relationship is not a pure systolic contractility index but rather integrates both systolic and diastolic properties. Therefore, the PRSW relationship can be considered as a measure of integrated pump function.

Limitations

Data were prospectively acquired and retrospectively analyzed, with the inherent limitations of this study design. The stressor used (exercise, dipyridamole or dobutamine) was chosen on the basis of specific contraindications, local facilities and physician's preference. The contractile response evoked by dipyridamole is clearly less than that induced by dobutamine, but the use of lower cut-off values of LVCR for dipyridamole (<1.1) allows to identify prognostically significant forms of coronary and/or myocardial disease with the same accuracy as the 2.0 cut-off value adopted for dobutamine and exercise stress (8, 9). The prognostic value of the Mw slope at rest was similar to that obtained during stress. This suggests that, theoretical considerations aside, it is not worthwhile to assess this parameter during stress. For prognostic stratification, the best combination is obtained with Mw at rest and LVCR stress assessment. We observed a high number of events (132/692, 19%). There were 57 heart failure hospitalizations, because of the high number of patients with IDCM and severe left ventricular dysfunction: 117 (53%) of 222 IDCM patients had LVEF < 30%, and 16 out of the 57 IDCM hospitalized patients underwent cardiac resynchronization therapy. Obviously, standard resting LVEF was a powerful predictor of future cardiovascular events, showing a significant cutoff value < 35% (area under the curve 0.732, 95% CI 0.676-0.787; positive predictive value 82%, negative predictive value 60%; youden index = 1.416). The LVCR assesses contractile reserve which is usually evaluated through the improvement in LVEF. However, LVCR is profoundly different from LVEF from a conceptual, methodological and clinical point of view. It is independent from preload and afterload changes (3), which affect LVEF; it requires only measurement of systolic blood pressure by cuff sphygmomanometer and end-systolic volume by 2D echocardiography, rather than end-diastolic and end-systolic volume; and is more prognostically powerful than LVEF changes in identifying patients at higher risk both with normal and markedly abnormal resting left ventricular function (2), with all forms of stress -exercise, dobutamine and dipyridamole (2). We applied the novel contractility indices to a wide range of different patients studied with different stresses in different labs and with a spectrum of underlying baseline resting left ventricular function. Therefore, the broad selection criteria led to a substantial heterogeneity of recruitment, although they also witness that the methodology can be applied to different geometry and function models.

Clinical implications

Triple contractile imaging is highly feasible during SE. Triple contractile imaging SE is technically simple, does not require additional technology or software, only minimally increases the analysis time, and allows effective risk stratification in patients, more powerful than that achieved with single or dual contractile imaging alone. In patients with negative SE by RWMA, the best prognostic stratification is obtained with resting Mw and stress LVCR.

CONCLUSIONS

In conclusion, the PRSW relationship slope can be estimated from a steady-state beat without alteration of preload. This technique is not significantly affected by different left ventricular sizes, left ventricular mass, and the presence of RWMA and has the potential for noninvasive applications during resting transthoracic echocardiography. Triple imaging assessment of contractility with RWMA, LVCR and the resting PRSW relationship slope offers potentially important and additive clinical information with only minimal increase in analysis time and without need of extra software.

Conflicts of interests

None declared.

(See authors' conflicts of interest forms on the web/Supplementary material).

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